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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

E. Raspe et al. : Examiner: S. Chunduru

Serial No.: 09/646,924 : Group Art Unit: 1656

Filed: September 25, 2000 :

For: **USE OF ROR RECEPTORS FOR SCREENING SUBSTANCES USEFUL FOR THE TREATMENT OF ATHEROSCLEROSIS**

APPEAL BRIEF

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Further to the Notice of Appeal filed January 2, 2003, herewith are three copies of Appellants' Brief on Appeal. A check for the statutory fee of $320.00 fee for filing an Appeal Brief and the $410.00 fee for a two-month extension of time is enclosed. This is an appeal from the decision of the Examiner finally rejecting claims 1, 3-12 and 14-22 of the above-identified application.

(1) REAL PARTY IN INTEREST

The real party in interest in the present application is Merck Patent GmbH, to whom the present application is assigned, the Assignment being recorded November 21, 2000, at Reel 011297, Frame 0713.

(2) RELATED APPEALS AND INTERFERENCES

There are no known related appeals or interferences.

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I hereby certify that this correspondence is being deposited with the U.S. Postal Services as First Class Mail in an envelope addressed to: Assistant Commissioner For Patents, Washington, D.C. 20231 on: 5/2/03
Name: Janet M. Jacobs
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Date: 5/2/03

(3) STATUS OF THE CLAIMS

During the prosecution of the instant application, claims 1-22 were presented for examination. Claims 2 and 13 were cancelled in the Reply Under 37 CFR §1.116, filed November 1, 2002. Claims 1, 3-12 and 14-22 remain pending. All of these pending claims stand rejected. A copy of all the pending claims is presented in the Appendix.

(4) STATUS OF AMENDMENTS AFTER FINAL

All Amendments have been entered, including the After-Final Amendment of November 1, 2002.

(5) SUMMARY OF THE INVENTION

The invention relates to primarily to methods of using RORα receptor, or a response element thereof involved in the regulation of the apo C-III gene (page 5, lines 1-31; page 6, lines 34-39, etc.), as well as methods related to regulating the apo C-III gene by binding entities to the mentioned receptor and/or response element (page 5, lines 15-31, page 12, lines 14-35, etc.).

(6) ISSUES

The sole issue on appeal concerns whether the phrase "response elements thereof" is supported under 35 U.S.C. §112, first paragraph by a written description in the specification. (See item 5 of the Examiner's Advisory Action of February 19, 2003 and paragraph 4 of the Final Rejection of July 1, 2002.)

(7) GROUPING OF THE CLAIMS

All claims stand or fall together.

(8) APPELLANTS' ARGUMENTS

The Examiner has explained the sole remaining issue for the first time in the Advisory Action of February 19, 2003:

> "The instant specification broadly describes a response element with no structural limitation and the phrase response elements thereof [sic] includes several response elements which are not disclosed in the instant specification. Therefore, the rejection under U.S.C. §112[sic], first paragraph is maintained herein."

This is an untenable basis for a rejection under the first paragraph of 35 U.S.C. §112. Firstly, the specification, contrary to the quoted statement, does disclose plentiful structurally defined response elements. See the following disclosures in the specification:

> "The response element used in step (b) may for example consist of the fragment of the apo C-III promoter between positions 1415 and +24." (page 8, lines 10-12); (see also page 22, lines 37-39.)
>
> * * *
>
> "a) a plasmid is created which comprises several copies of a response element recognized by ROR such as for example the consensus site described by M. Lazar (43)," (page 9, lines 14-17)
>
> * * *
>
> "The construct RORETkCAT which comprises a copy of the hRORα consensus response element has been previously described (53)." (page 13, lines 22-25)
>
> * * *
>
> "This observation suggests the presence of an hRORα1 nuclear receptor response element in the –1415/+24 portion of the promoter of human apo C-III." (page 22, lines 37-39)

* * *

"whose sequences correspond to the consensus response element of hRORα1 (RORECons) and to the half-site AGGTCA present downstream of the TaTa box of the human apo-C-III gene (hCIII-TaTaWT) (strong)." (page 28, lines 21-25)

* * *

"the gel retardation experiments confirm the interaction of hRORα1 with the portion between positions –198 and +24 of the apo C-III promoter and suggest the existence of two binding sites: the half-site AGGTCA situated downstream of the TaTa box (-23/-18) and the half-site AGGTCA present in 5' of the C3P site (-77/-82)." (page 30, lines 33-39)

* * *

"d. Analysis of the response elements isolated from the apo C-III promoter cloned upstream of the TK promoter" (page 32, lines 6-38, only lines 6-8 being reproduced above, the remainder of page 32 of the specification being attached as Appendix II)

As is clear, the specification is replete with examples of structurally defined response elements. It is respectfully submitted that the Examiner is incorrect in this regard.

Given this true assessment of the specification's content, under clear U.S. law, there is no doubt that the current claims have a full written description in the specification. For example, where a functional expression such as that at issue is recited in a claim, the written description requirement "may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." Amgen v. Hoechst 314 F.3d. 1313 at 1332, 65 USPQ2d 1385 (Fed. Cir. 2003). Under the current facts, not only is there a particular known structure involved, but several are defined in the specification. This more than meets the requirements set forth by the

Federal Circuit. Furthermore, it is also the PTO's own position that, where a term is used in a claim and encompasses more than one possibility, there is a written description as long as there is a known correlation between structure and function. (See the PTO's Written Description Guidelines.)

Finally, the Examiner also implies that the claims are somehow defective because they encompass "several response elements which are not disclosed in the instant specification." However, if this were the law, then claims of any reasonable scope would rarely be granted. Of course, this is not the case. It has always been the law that a patent specification need merely "exemplify" the claims, not provide litanies of descriptions of all possible varriations. (See, *In re Angstadt*, 537 Fed 2d. 498, 190 USPQ 214 (CCPA 1976).

(9) Conclusion

The claims do have a perfectly adequate written description in the specification under Federal Circuit precedent in view of the foregoing facts.

In view of the arguments and authorities presented above, Appellants request that the Examiner's action in making and maintaining the Rejection under 35 USC §103 be reversed and that the application be allowed.

Respectfully submitted,

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APPENDIX I

1. (Twice Amended) A method of screening a substance for usefulness in the treatment of a lipid metabolism dysfunction comprising contacting said substance with a ROR α receptor, or a response element thereof involved in the regulation of the apo C-III gene, and measuring the level of apo C-III gene expression.

3. (Twice Amended) A method of screening a substance for usefulness in the treatment of a lipid metabolism dysfunction, comprising contacting said substance with (a) a ROR α receptor involved in the regulation of the expression of the apo C-III gene, (b) a response element of a ROR α receptor, or (c) a nuclear factor which functionally couples ROR α to a RNA polymerase complex, and then measuring:

i) the binding of said substance to the ROR α receptor or the binding of the complex formed by said substance and the ROR α receptor to its response element or to a nuclear factor which couples ROR α to a RNA polymerase complex;

or

ii) the modulation of the transcriptional activity of a gene placed under the control of a promoter comprising said response element.

4. (Twice Amended) The method of screening according to claim 3, comprising:

a) transfecting a cellular host with a DNA fragment encoding an ROR α receptor;

b) cotransfecting the host in a) with a construct comprising a response element of said ROR α receptor and at least one reporter gene; and

c) measuring the expression of the reporter gene in the presence of the test substance.

5. (Twice Amended) The method of screening according to claim 3, comprising:

a) creating a plasmid which comprises several copies of a response element recognized by ROR α cloned upstream of a strong heterologous promoter which controls the expression of a reporter gene;

b) transfecting the construct of a) into host cells which express ROR α naturally or artificially;

c) incubating the host cells of b) in the presence of the test substance; and

d) measuring the activity of the reporter gene.

6. (Twice Amended) The method of screening according to claim 3, comprising:

a) creating a plasmid which comprises several copies of a response element recognized by ROR α cloned upstream of a promoter which controls the expression of a selectable gene;

b) transfecting the construct of a) into a cellular host;

c) cotransfecting the host of b) with the aid of a vector expressing ROR α;

d) incubating the host of c) in the presence of the test substance; and

e) measuring the cellular survival of said cellular host in the presence of a toxic prodrug.

7. (Twice Amended) The method of screening according to claim 3, comprising:

a) creating a plasmid which comprises several copies of a response element recognized by a yeast nuclear factor Gal4 cloned upstream of a strong promoter which controls the activity of a reporter gene;

b) creating a plasmid from a chimera which comprises a DNA binding domain of Gal4 and a DEF domain of ROR α which are the ROR α domains to which the ligands bind;

c) cotransfecting the plasmids in a) or b) into a cellular host;

d) incubating the host of c) in the presence of a test substance; and

e) measuring the activity of said reporter gene.

8. (Twice Amended) The method of screening according to claim 3, comprising:

a) transforming the cellular host with a construct carrying a gene encoding a ROR α receptor or a response element of a ROR α receptor, and;

b) assaying said cellular host or an extract thereof for the competitive displacement in the binding of labeled and unlabeled ligand to said ROR α receptor.

9. (Twice Amended) The method of screening according to claim 4, wherein the construct carrying the gene encoding a ROR α receptor or a response element of the ROR α receptor also comprises a reporter gene.

10. (Amended) The method of screening according to claim 9, wherein the reporter gene is chosen from chloramphenicol acetyltransferase, the gene for luciferase from firefly or from Renilla, the gene for secreted alakaline phosphatase, the gene for beta-galactosidase or the gene for apo C-III.

11. (Amended) The method of screening according to claim 4, wherein the cellular host is chosen from mammalian cells, bacteria, yeasts, or insect cells.

12. (Amended) The method of screening according to claim 3, wherein the effect of said substance on the expression of said apo C-III gene is determined using transfection or analysis of mRNAs *in vitro* or on models *in vitro* or *in vivo*.

14. (Amended) A method for preparing a pharmaceutical composition or a medicament useful in treating or preventing atherosclerosis in humans or animals comprising selecting a substance screened according to claim 3.

15. (Amended) A method for treating or preventing atherosclerosis in humans or animals comprising modulating the expression of apo C-III using a medicament or a pharmaceutical composition comprising a substance selected according to claim 3.

16. (Twice Amended) A method for treating or preventing atherosclerosis in humans or animals comprising administering a medicament or a pharmaceutical composition comprising a substance which binds to a ROR α receptor, or its response element involved in the regulation of the apo C-III gene.

17. (Amended) The method according to claim 3, wherein the substance has antiatherosclerotic properties.

18. (Amended) A method of screening according to claim 8, wherein the construct carrying a gene encoding the ROR receptor or a response element of the ROR receptor also comprises a reporter gene.

19. The method according to claim 1, wherein the lipid metabolism dysfunction is atherosclerosis.

20. The method according to claim 2, wherein the lipid metabolism dysfunction is atherosclerosis.

21. The method of screening according to claim 4, wherein the lipid metabolism dysfunction is atherosclerosis.

22. (Amended) A method of measuring the expression of the apo C-III gene, comprising contacting a substance with a ROR α receptor or a response element of the ROR α receptor involved in the regulation of the expression of the apo C-III gene or a response element of the ROR α receptor or a nuclear factor which couples ROR α to a RNA polymerase complex, and then measuring:

i) the binding of said substance to the ROR α receptor or the binding of the complex formed by the said substance and the ROR α receptor to its response element or to a nuclear factor which couples ROR α to a RNA polymerase complex;

or

ii) the modulation of the transcriptional activity of a gene placed under the control of a promoter comprising said response element.

combination of the same mutation with the mutation of the half-site AGGTCA present at position 3' of the C3P site (construct -1415/+24hCIIITaTa+C3P3'KOLuc+) appears to accentuate the loss of sensitivity of the promoter with respect to hRORα1.

d. Analysis of the response elements isolated from the apo C-III promoter cloned upstream of the TK promoter

In Figure 12, 10,000 RK13 cells were plated per well of a 24-well culture plate and transfected with the aid of a cationic lipid with 50 ng/well of reporter vectors $(-30/-15)_n$TkpGL3, $(-76/-100)_{2x}$TkpGL3, $(-27/-59)_{5x}$TkpGL3, $(-59/-27)_{8x}$TkpGL3, (-47/-79)TkpGL3 and TkpGL3 (negative control) as indicated, 100 ng/well of expression vector pCDNA3 or pCDNA3-hRORα1 as indicated and 50 ng of vector pSV-βgal. The total quantity of transfected DNA was brought to 500 ng/well with the aid of the plasmid pBluescript used as carrier. After incubating 36 hours, the cells were rinsed, lysed and the luciferase activity of the cellular extracts assayed with the aid of the "Dual-Luciferase™ Reporter Assay System" kit from Promega. The β-galactosidase activity of the cellular extracts was measured according to the conventional protocol (31).

The Figure 12 shows that the half-site AGGTCA present downstream of the TaTa box of the apo C-III gene cloned upstream of the Tk promoter (construct (-30/-15)hCIIITkpGL3) is activable by hRORα1. Outside the context of the human apo C-III promoter, this site which is identified by gel retardation is functional. The construct which comprises two copies of the fragment -76/-100 (half-site AGGTCA 3' of the C3P site included) (construct $(-76/-100)_{2x}$hCIIITkpGL3) cloned before the Tk promoter is also activated by hRORα1. The constructs which comprise other fragments of the proximal promoter of human apo C-III between the TaTa box and the C3P site cloned before the Tk promoter are insensitive to hRORα1.

e. Conclusions